ATTACHMENT 8

Expert Report on the Pharmaco-Toxicological (Pre-Clinical) Documentation of Humet-R Syrup

1999

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INTRODUCTION

HUMET-R SYRUP is a roborating product for macro- and microelement supplements.

Humic acids and 16 kinds of amino acids compose the carrier part of the product, which is enriched with essential macro and micro elements . Ten ml flavoured syrup contains total amount of 75 mg humic acid, 36 mg potassium, 15 mg magnesium, 14 mg iron, 10 mg zinc, 3mg manganese, 0.5 mg vanadium, 0.2 mg cobalt, 0.17 mg molybdenum, and 0.13 mg selenium. The recommended daily oral dose for adult is 10 ml syrup. Metals are bound through multiple chelate bonds to the polypeptides and phenol carbonic acids are connected to the heteroaromatic nucleus.

Therapeutic indications are followings:

-It is a general roboration in convalescence periods.

-For elderly people the product helps tracing element deficiency conditions.

-Humet-R helps strengthening resistance of the organism and preventing diseases in epidemic periods.

-It improves mental and physical performance.

-The product ceases iron deficiency.

-It supplements iron in conditions with blood loss (e.g. in women's period

Humet-R is on market since 1993. It has been approved by the Hungarian National Institute of Pharmacy and it has been registered under OGYI 430/1993 number in the OTC category. It is also registered in the following countries: Slovak Republic, Belarus, Russia, and Ukraine and is submitted for registration in Canada, Lithuania, and Yemen Republic.

TOXICITY

Single dose toxicity

Humet: Acute oral toxicity study in the rat

(See: attached Table of Contents of tabulated study reports and Tabulated Study Reports on Page:1)

According to the first non GLP single dose toxicity test in rats, no sign of toxicity and no death occurred even in the 10000 mg/kg treated group. It was estimated that the LD_{50} dose of Humet is over 10 g/kg.

Usually drugs which cause no sign of toxicity or death in 2000-5000 mg/kg dose could be considered as no toxic. However, doses were calculated in case of this first non GLP toxicity to the whole amount of the finished product.

Acute oral toxicity of supplemented humic acid (DHS) in two species mice and rats

(see:Tabulated study report Page:2-3)

Intrinsic safety profile of Humet R in single dose was more precisely demonstrated by acute oral toxicity "limit tests" using mices and rats. "Limit test" is usually used in case of non toxic substances. The test is designed for two groups: control and treated and treated group should have used the highest applicable dose. In case of Humet-R the highest dose was limited by the applicable highest volume (40 ml/kg). This was 4 times higher then in (non GLP) preliminary one at both species. No death or toxic symptoms occurred after the treatment and during the 14 days observation period. It was considered that the minimal toxic dose and LD_{50} are above 40 ml/kg Humet-R syrup which is equivalent of 600 mg/kg active ingredients content calculated for humic acid and also equivalent of 2292 mg/kg of dry matter of the product.

Repeated dose toxicity

Effect of prolonged dose on rats

(See: Tabulated study report Page 4)

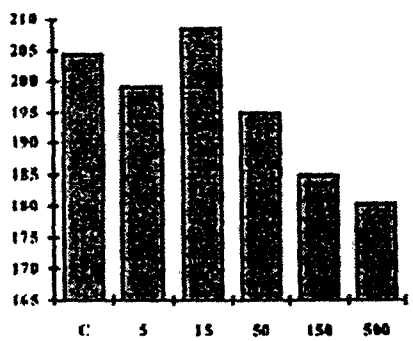
A 28 days non GLP study was conducted in order to clarify the possible side effects of Humet-R after repeated administration. To achieve a high and wide concentration range Humet-R was mixed into the normal rat food in a syrup free condition and rats were fed for 28 days in the following doses: 5, 15, 50, 150, 500 mg/kg. It was estimated that rats consume 20g food pro day. Ten female animals were used in the experimental groups. The control group was supplied by normal rat food.

Animals were observed daily, body weight was measured weekly, and parameters of clinical chemistry, hematology and organ weights were measured at the time of necropsy. Deviations from a regular type repeated dose toxicity study is the following: only one sex was used. Measuring of food consumption, water consumption, urinalysis and histological evaluation were not employed.

No death occurred during the treatment. Body weight gain decreased from the 3rd week in 150 and 500 mg/kg treated groups dose dependently. Body weight, kidney and liver

weights were significant lower in the same groups at the end of the study. No other change could be detected by hematology or clinical chemistry. It can be stated that NOEL and NOAL are over the oral 50 mg/kg dose in female rats.

In the following chart body mass changes are demonstrated after a 4-weeks feeding of syrup-free HUMET®-R on female rats (ten animals each per group, C = Control). Ordinate: Body mass group means in gram. Abscissa: syrup-free Humet-R humic dose in mg/kg. In 150 and 500 mg/kg treated groups body weight were decreased ($P < 0.05$) compared to the untreated control group.



Mutagenicity

Reverse mutation assay in Salmonella typhimurium

(see: Tabulated study report Page 5-9)

Investigating reverse mutation assay using Salmonella typhimurium tester strains assessed mutagenic potential of HUMET-R. Mutagenic activity was evaluated by measuring reversion of histidine auxotrophs to prototrophs.

Results of the study showed that Humet-R did not induce increases in the number of revertant colonies at any dose-level, in the five salmonella strains, either in the absence or presence of S9 metabolism. The test substance had no mutagenic activity and no bactericide effect under the reported experimental conditions. (≤.7500 µg testsubstance /plate with preincubation)

According to the corresponding CPMP/ICH/141/95 guideline "Genotoxicity: Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals", the recommended highest concentration is 5000 µg testsubstance /plate.

Clastogenic and anticlastogenic effect

(see: Tabulated study report Page 10-11)

The clastogenic and/or the possible anticlastogenic properties of the Humet-R were reported in two in vitro mutgenicity tests on human lymphocytes. Even in much higher concentrations than the physiological dose Humet-R did not reveal chromosomal damage. The anticlastogenic effect was investigated in the second step using 200 rad x-ray to induce chromosomal aberration in human lymphocytes at much lower Humet concentrations (protective agent) in media. Although the number of di-centric ring aberrations decreased together with decreasing of Humet-R concentration, number of aberrant cells decreased only at one intermediate concentration of Humet. However, the result suggests certain condition in vitro anticlastogenic effect of Humet but this can not be considered as a proven fact.

PHARMACODYNAMICS

Effect of supplemented and un-supplemented humic acids on the metabolic balance in rats.

(see: Tabulated study report Page 12)

Three groups of female Wistar rats were tested. Two groups were gavaged daily by gastric tube with supplemented and un-supplemented humic acid for 31 days.
At the end of the experiment animals were killed. After extirpation of the stomach and intestine rest of the body was incinerated. The ash solutions were investigated with atomabsorption analysis. The whole body content of Ca, Mg, Mn, Cu, Zn and Fe were determined. As a result of the above mentioned test, supplemented humic acid treatment increased the whole body contents in Fe, Ca, and Mg.

Effect on iron deficiency

(see: Tabulated study report Page 13-16)

Aim of the study was to determine the effectiveness of different formulations of macro and micro elements supplemented humic acids in the treatment of iron deficient rat pups. During the whole gestation and lactation period and thereafter up to the offspring's 21st day, normal control offspring and their mothers were fed with normal rat food while other dams and their offspring were fed with iron deficient diet (< 5 ppm). Six groups of iron deficient offspring were configured, five of them were treated with different formulation of supplemented humic acid. All formulas of the macro and micro elements supplemented humic acid proved to be effective in improvement of the general status and laboratory parameters in iron deficient animals. The effect was comparable to Aktiferrin. The best result was achieved by the Humet-R syrup treatment (Gr4.). Even the serum triglicerride level normalised in this group up to the end of the study, while it left low after the Aktiferrin treatment

Effect on systemic ^{85}Sr and ^{103}Ru pollution

(see: Tabulated study report Page 12)

Aim of the study was to investigate the effect of Humet-R treatment in systemic exposition of radioactive ^{85}Sr and ^{103}Ru salts. Animals were treated with radioactive $^{85}SrCl_2$ in a 250 µg/kg (3.7 MBq/kg) oral or parenteral (i.p.) dose or ^{85}Sr was applied in humic acid complex. while ^{103}Ru salt ($(NH4)_2Ru[(H2O).Cl_5]$ was applied orally in 90.9 mg/kg (1.91 MBq/kg) dose alone or in humic acid complex.

Conclusions:

Group 1-2: (Aim: determination of radioactivity in faces and urine after one p.o. dose of ^{85}Sr salt and ^{85}Sr-humic acid complex)

The cumulative urinary excretion of $^{85}SrCl_2$ treated animals at 96 hours: 2,87 ± 0,65. (% of dose).

The cumulative urinary excretion of ^{85}Sr-Humic a. complex treated animals at 96 hours: 1,59± 0,42 (% of dose). Explanation: Less ^{85}Sr were absorbed from the complex than from the solution.

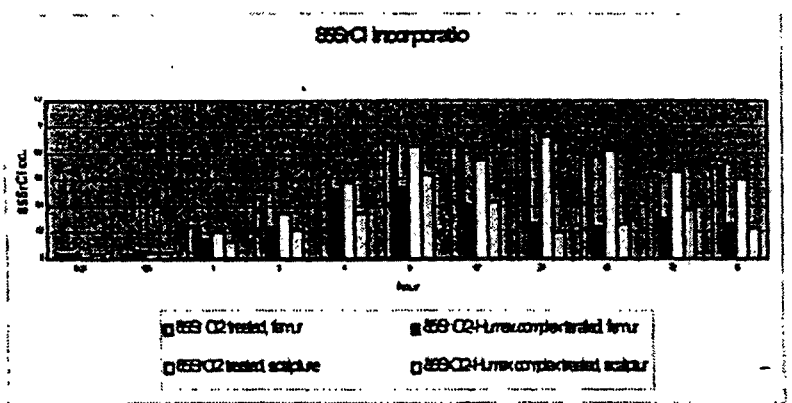
Less quantity of radioactivity was eliminated via the stool in the first 24 hours in animals treated with ^{85}Sr-Humic a complex. By the 96th hours, the difference between the two groups eliminated.

Group 3-5: (Aim: determination of radioactivity in faces and urine after one i.p. dose of ^{85}Sr salt and 24 hours thereafter one or four times repeated p.o. dose of ^{85}Sr-humic acid complex)

Oral administration of humic acid (once or repeatedly) did not influence the urinary and faecal excretion of ^{85}Sr.

Group 6-7: (Aim: determination of radioactivity in tissues of 16 organs urine after one p.o. dose of ^{85}Sr salt and ^{85}Sr-humic acid complex at 12 times)

Significant less ^{85}Sr incorporated in to the bones at ^{85}Sr-Humic a. complex treated animals than at $^{85}SrCl_2$ solution treated ones after 96 hours of the threatment .



Group 8-9: (Aim: determination of radioactivity in faces and urin after one p.o. dose of ^{103}Ru salt and ^{103}Ru-humic acid complex)

There were no detectable differences in urinary and faecal excretion of ^{103}Ru between animal treated with the ^{103}Ru salt solution alone or with the ^{103}Ru -complex.
Less amount of radioactivity was found in the tissues of animals treated with the complex preparation than in the control.

It is supposed that less ^{103}Ru were absorbed from the complex than from the solution.

Cardioprotective effects

(see: Tabulated study report Page 19-20)

Cardiac failure and arrhytmias have particular role in mortality of patients suffering from ischemic heart disease. The most significant biochemical mechanism is generation of oxygen free radicals at the onset of reperfusion. This underlines the manifestation of ventricular fibrillation. It was supposed that selenium and humic acid may play a protective role with encouragement of antioxidant mechanisms.

The cardioprotective and antiarrhytmic effects were studied on isolated working rat heart after 2 weeks oral treatment with 30 mg/kg humic acid and 10 and 30 mg/kg Humet-R. Both humic acid and Humet-R showed some cardiprotective effects on ischemic myocardium, and no effect on nonischemic myocardium.

The most significant cardioprotective and strong antiarrhtmic effects were caused by the 2 weeks treatment with 10 mg/kg Humet-R. The mechanism can not be answered on the basis of this study but anti oxidant mechanism could be supposed.

Effects on the sexual activity

(see: Tabulated study report Page 21)

Research of compounds increasing sexual activity (aphrodisiacs) requires appropriate experimental models. Principle of the method developed by the author's team:

an appropriately long 'deprivation' makes adult male rats chronically unable to display the complete sexual behavioural pattern (mounting, intermission, and ejaculation) even if a receptive female is present. During the weekly mating check-ups, such males behave either sexually inactively (show no copulatory pattern at all), became 'mounting-only', or they were 'sexually lazy' males who were incapable of intermission and/or ejaculation. If an aphrodisiac treatment is really efficient, male rats selected in this way will again display the complete mating behaviour in the presence of a receptive female. This method had allowed the discovery of the aphrodisiac effect of deprenyl, a world-wide known drug (Jumex, Movegan, Eldepryl) employed with success in Parkinson and Alzheimer's disease.

The other way employed by author was the selection of sexually inactive dotard (10-30 month old) male rats. Definition: sexual inactivity was confirmed at male rats who did not

show any reaction (mounting, intromission, ejaculation) at presence of recipient female one after other four challenges.

The effect of Humet-R and different solutions of Humet-S were studied on different aged adult and dotard sexually inactive male rats.

At the first experimental series 10 months old sexually inactive male rats were investigated. Eight animals were treated daily with Humet-R in a dose of 1 ml/animal for 15 weeks, as a contrast of 10 control animals were treated with 1 ml of 5% glucose. The treatment was followed by a 30 weeks post-treatment observation period. The sexual challenge was employed once a week for 30 minutes.

All Humet-R treated males become sexually active during the treatment period and full copulatory repertoire could be detected up to the end of post-treatment observation period. The sexual agility developed at eight males with the following latency: 1,3,4,4,4,11,13,17 weeks respectively. Two males become also sexually active in the control group but loosed their sexual ability during the post-treatment period.

Humet-S was investigated in a series of experiments employed different doses (0.1, 0.25, 1 ml animals) and different aged (10-30 month old) sexually inactive male rats. Results were similar to Humet-R. After a shorter latency period, one-third to half of the males recovered their sexual activity.

Even in case of three 30 months old dotard one recovered and displayed full scale of copulation after the fourteenth treatment. This result is quite surprising because a male rat looses his ejaculatory ability at age of 24 months.

CONCLUSIONS:

Considering all the pharmacological pattern and toxicological character achieved on laboratory tests and animals it is concluded that the oral administration of Humet-R in the recommended dosages will not produce any toxic effect.

From the pharmacological point of view Humet-R can be used according to the therapeutic indications and will become effective in strengthening conditions as roborant.

L. Ahmed Kali

February 8 1999

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f Company : ON-MULTIPLAN Ltd. f Finished Product : IUMET-R SYRUP SYRUP f Active Ingredient : acid, Potassium, Magnesium, Iron, Zinc, ese, Copper, Vanadium, Cobalt, Molybdenum, in	TABULATED STUDY REPORT ref.to III.A.11.0 Page / Number 1 / 1	
.E DOSE-TOXICITY	HUMET: ACUTE ORAL TOXICITY STUDY IN THE RAT	

do ent : HUM 001 Volume : Page : — to Addendum No. : —
t d : 6 November 1990 Number : 2148/1/90/OET1 Study period (years) : 1990

s/Strain : Rats, H-Wistar — Number of animals : 84

istration route : oral gavage by gastric tube — Dose [mg/kg] : max. non lethal : 10000; min. lethal : >10000

ment of controls : ap water — Observation period : (Appl.day = Day 1) 15 days

roup:	(1)		(2)		(3)		(4)		(5)		(6)	
: m	0		3000		4100		5500		7400		10000	
/f)	m	f	m	f	m	f	m	f	m	f	M	f
al/ ve	7	7	7	7	7	7	7	7	7	7	7	7
V. hours	0	0	0	0	0	0	0	0	0	0	0	0
7- hours	0	0	0	0	0	0	0	0	0	0	0	0
Day 2-7	0	0	0	0	0	0	0	0	0	0	0	0
Day 8-end of observ.	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0	0	0

mary of salient findings :

inis product of Humet was used as test item, 18 hours starvation was employed before the treatment

1-6: No toxic symptoms, no death, no treatment related finding at the autopsy

conducted by the applicant : [ ] Yes [x] No

o", indicate the name and address of the institute that conducted the study :
ONAL INSTITUTE OF FOOD AND NUTRITION SCIENCE Gyáli út 3/a 1097 Budapest, Hungary.

y in compliance with GLP : [ ] Yes [x] No [ ] Not required

Name of Company : HORIZON-MULTIPLAN Ltd **Name of Finished Product :** HUMET-R SYRUP **Name of Active Ingredient :** Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese. Copper, Vanadium, Cobalt, Molybdenum, Selenium	**TABULATED** **STUDY REPORT** **ref. to III.B.110** **Page / Number** 1 / 1	

REPEATED DOSE TOXICITY	HUMET-R: Effect of prolonged oral dose on rats

Ref. to document : HUM 032 Volume: Page : — to — Addendum No. : —
Report date : March 30 1994 Number : Study period (years) : 1994

Species/Strain : RAT, WISTAR Females

Number of animals : 60	**Duration of treatment : 28 days**
Observation period after the end of dosing : 0	
Administration route: by food	
Treatment of controls : Group I: Untreated, on normal food	**Age : at study** **Body weight : 150-170 g initiation**
	Treatment days per week : 7

Study group	control	Humet-R 5 mg/kg	Humet-R 15 mg/kg	Humet-R 50 mg/kg	Humet-R 150 mg/kg	Humet-R 500 mg/kg
Sex (m/f)	f	f	f	f	f	f
Number of test animals	10	10	10	10	10	10
Number of animals died or sacrificed in extremis	0	0	0	0	0	0

Clinical observations :	[x] yes	[ ] no	**Clinical chemistry :**	[x] yes	[ ] no
Food consumption :	[ ] yes	[x] no	**Urinalysis :**	[ ] yes	[x] no
Water consumption :	[ ] yes	[x] no	**Organ weights :**	[x] yes	[ ] no
Body weight :	[x] yes	[ ] no	**Necropsy :**	[x] yes	[ ] no
			Histology :	[ ] yes	[x] no

Additional information: doses and food consumption were calculated for 20g / animal / day

Conclusions: - Body weight gain decreased from the 3rd week in 150 and 500 mg/kg treated groups. Body kidney and liver weight were significant lower in the same groups at the end of the study.

Histology performed according to EEC Note for Guidance : [ ] Yes [x] No
Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Dep. of Toxicology, Health Institute of Hungarian Army, 1456 Budapest, Pf. 19., Hungary, Europe

Study in compliance with GLP : [ ] Yes [x] No [ ] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.D.110 Page / Number 1 / 5	

MUTAGENIC POTENTIAL **In vitro** REVERSE MUTATION IN SALMONELLA THYPHIMURIUM

Ref. to document : HUM 008 **Volume :** **Page :** — **to** — **Addendum No. :**—
Report date : 1 Oct. 1992 **Number :** 92/134-007M **Study period (years) :** 1992

Test cells : SALMONELLA THYPHIMURIUM TA 98
Test for induction of : base substitution and frameshift point mutation
Metabolizing system : Aroclor 1254 induced rat liver S 9-mix

Formulation of test substance and final concentration :
a) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate
b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate

Treatment and recovery time :
a) 48 hours, no recovery time
b) 48 hours, no recovery time

Solvent and Final concentration :
a) 1% aqueous potassium-pyrophosphate
b) 1% aqueous potassium-pyrophosphate

Formulation of positive Control and final Concentration
a) 4-nitro-o-phenilenediamine; 4 µg/plate
b) 2-Aminoanthracene; 4 µg/plate

Number of independent experiments :
a) 2 (without metabolic activitation)
b) 2 (with metabolic activitation)

Number of replicate cultures :
a) 3 plates per concentration
b) 3 plates per experiments

Number of cells analysed per culture :
a) —
b) —

Cytotoxic effects :
a) —
b) —

Genotoxic effects :
a) The test substances did not induce increases in the number of revertant colonies
b) Similar to the control values at any dose-level, either in the absence or presence of S9 metabolism

Effects of the positive control :
a) 2142 plate counts (exp.1) resp. 584 (exp.2); solvent control 34 (exp.1) resp. 34 (exp.2)
b) 3221 plate counts (exp.1) resp. 384 (exp.2); solvent control 39 (exp.1) resp. 38 (exp.2)

Additional data regarding methods and time schedule of the test :
-Test item was the lyophised form of the finished productwith a 78.5 g/l of dry remnant content
-To demonstrate mutagenic effect the concentration of S9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study.

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Toxicological Research Centre Ltd. Szabadságpuszta Veszprém H-8200 Hungary EUROPE

Study in compliance with GLP : [x] Yes [ ] No [ ] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to IILD.110 Page / Number 2 / 5	

MUTAGENIC POTENTIAL	In vitro	REVERSE MUTATION IN SALMONELLA THYPHIMURIUM

Ref. to document : HUM 008 Volume : Page : — to — Addendum No. :—
Report date : 1 Oct. 1992 Number : 92/134-007M Study period (years) : 1992

Test cells :	SALMONELLA THYPHIMURIUM TA 100
Test for induction of :	base substitution and frameshift point mutation
Metabolizing system :	Aroclor 1254 induced rat liver S 9-mix

Formulation of test substance and final concentration :	a) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate
Treatment and recovery time :	a) 48 hours, no recovery time b) 48 hours, no recovery time
Solvent and Final concentration :	a) 1% aqueous potassium-pyrophosphate b) 1% aqueous potassium-pyrophosphate
Formulation of positive Control and final Concentration	a) Methyl methane sulphonate; 2 µg/plate b) 2-Aminoanthracene; 4 µg/plate

Number of independent experiments :
a) 2 (without metabolic activitation)
b) 2 (with metabolic activitation)

Number of replicate cultures :
a) 3 plates per concentration
b) 3 plates per experiments

Number of cells analysed per culture :
a) —
b) —

Cytotoxic effects :
a) —
b) —

Genotoxic effects :
a) The test substances did not induce increases in the number of revertant colonies
b) Similar to the control values at any dose-level, either in the absence or presence of S9 metabolism

Effects of the positive control :
a) 1454 plate counts (exp.1) resp. 1096 (exp.2); solvent control 133 (exp.1) resp. 141 (exp.2)
b) 2028 plate counts (exp.1) resp. 799 (exp.2); solvent control 143 (exp.1) resp. 147 (exp.2)

Additional data regarding methods and time schedule of the test :
-Test item was the lyophised form of the finisched productwith a 78.5 g/l of dry remnant content
-To demonstrate mutagenic effect the concentration of S9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study.

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Toxicological Research Centre Ltd. Szabadságpuszta Veszprém H-8200 Hungary EUROPE

Study in compliance with GLP : [x] Yes [ ] No [ ] Not required

Name of Company:
HORIZON-MULTIPLAN Ltd.
Name of Finished Product :
HUMET-R SYRUP
Name of Active Ingredient :
Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese. Copper, Vanadium, Cobalt, Molybdenum, Selenium

TABULATED
STUDY REPORT
ref.to III.D.110

MUTAGENIC POTENTIAL In vitro

ANTI-CLASTOGENIC EFFECT OF HUMET_R IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES

Ref. to document : HUM 004 Volume : Page : --- to --- Addendum No. :---
Report date : 1992 Number : Study period (years) : 1992

Test cells : Peripheral human lymphocytes
Test for induction of : Anticlastogenic effect
Metabolizing system : Non

Formulation of test substance and final concentration :
a) solution: 1, 2, 5, 10 µl / ml culture
b)

Treatment and recovery time :
a) 2 GY (200 rad) x ray, 48 hours incubation
b)

Solvent and Final concentration :
a) media: 10 ml RPMI-1640 + 0,8 ml blood + 0.2 ml Phytohemagglutinin M tp prepare cell division, after 48 hour 0.1 µg/ml colcemide to stop the cell division
b)

Formulation of positive Control and final Concentration
a) N /A
b)

Number of independent experiments :
a) 2
b)

Number of replicate cultures :
a)
b)

Number of cells analysed per culture :
a) 600 in control, 200 in treated groups-
b) ---

Genotoxic effects : Aberrations of chromosomal aberrations cell X ± SEM

	Chromatid break	chromosome break	dicentric ch + ring	aberrant cell
control	0.00	0.00	0.00	0.00
2 Gy control	0.01±0.001	0.29±0.002	0.42±0.002	0.41±0.002
Humet 10 µl / ml	0.01±0.001	0.24±0.002	0.40±0.002	0.41±0.003
Humet 5 µl / ml	0.0	0.25±0.002	0.37±0.003	0.26±0.003
Humet 2 µl / ml	0.01±0.001	0.27±0.002	0.36±0.003	0.35±0.004
Humet 1 µl / ml	0.0	0.25±0.002	0.33±0.003	0.38±0.003

Dicentric ring aberations decreased with the decrease of Humet cc., but a significantly lower value of aberrant cells was reached only in case of 5 µl / ml concentration

Effects of the positive control : a) N /A

Additional data regarding methods and time schedule of the test :

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Department of Human Genetics, Medical Research Institute 1138 Budapest Váci út 174 Hungary EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company :	TABULATED STUDY REPORT	
HORIZON-MULTIPLAN Ltd.		
Name of Finished Product : HUMET-R SYRUP	ref.to III.F.110	
Name of Active Ingredient : Humic acid. Potassium. Magnesium. Iron. Zinc. Manganese. Copper. Vanadium. Cobalt. Molybdenum. Selenium	Page / Number 1 / 1	
PHARMACODYNAMICS relating to proposed indication	The effect of supplemented and unsupplemented humic acids on the metabolic balance in rats	

Ref. to document : 33-1-03Volume : Page : --- to --- Addendum No. :—

Report date : Juni 10 1997 Number : Study period (years) : 1997

Experimental design:

Three groups of female Wistar rats were tested. Two groups were gavaged daily by gastric tube with supplemented and unsupplemented humic acid for 31 days.

At the end of experiment animals were killed. After the extirpation of the stomach and intestines the rest of the body was incinerated. The ash solution s were investigated with atomabsorption analysis. The whole body content of Ca, Mg, Mn, Cu, Zn and Fe were determined.

Results:

Groups	Ca (g/kg vet mass)	Mg (g/kg vet mass)	Mn (mg/kg vet mass)	Cu (mg/kg vet mass)	Zn (mg/kg vet mass)	Fe (mg/kg vet mass)
Control (No 8)	29,22 ± 3,05	1,02 ± 0,06	2,22 ± 0,21	4,54 ± 0,94	80,56 ± 2,5	133,3 ± 6,75
Humic acid 320 µl/kg unsupplemented * (No 9)	26,48 ± 3,01	0,97 ± 0,05	2,11 ± 0,28	3,94 ± 0,58	79,03 ± 3,83	121,1 ± 10,8
Humic acid 640 µl/kg supplemented * (No 9)	32,98 ± 4,03 ♣	1,1 ± 0,06 ♣	2,29 ± 0,2	4,99 ± 0,37	82,7 ± 5,33	148 ± 13,2 ♣

* = The concentration of supplemented humic acid solution was the half of the unsupplemented ones

♣ = P < 0.05 compared to the untreated control

Conclusions:

The unsupplemented humic acid treatment decreased the body contents in Fe, Ca, and Mg, while supplemented humic acid treatment increased the whole body contents in the same elements

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

Chemistry-Biochemistry, Pannon University of Agricultural Science, 7400 Kaposvár Guba S. u. 40. Hungary. EUROPE

Study in compliance with G.L.P : [ ] Yes [ ] No [x] Not required

Name of Company : HORIZON-MULTIPLAN Ltd.	TABULATED STUDY REPORT ref.to III.F.110	
Name of Finished Product : HUMET-R SYRUP		
Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	Page / Number 1/ 4	
PHARMACODYNAMICS relating to proposed indication	Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups	

Ref. to document : 42-1-11 Volume : **Page : —** **to —** **Addendum No. :—**

Report date : April 29. 1997 **Number :** **Study period (years) :** 1997

Experimental design:

Aim of the study was to determine the effectiveness of different formulations of macro and micro elements supplemented humic acids in the treatment of iron deficient rat pups. During the whole gestation and lactation period and thereafter up to the offspring's 21st day, normal control offspring and their mothers were fed with normal rat food while other dams and their offspring were fed with iron deficient diet (< 5 ppm) Six group of iron deficient offspring was configured, five of them were treated with diferent formulation of supplemented humic acid, as follows:

Experimental groups:

GR1. Normal control on normal diet	40 animals
Gr2. Iron deficient negative control on iron deficient (ID) diet	40 animals
Gr3. Aktiferrin treated (3.7 mg Fe/kg) positive control on ID diet	40 animals
Gr4. HUMET-R Syrup suspension (3.7 mg Fe/kg, humic a. 0.66 ml/kg), animals on ID diet	40 animals
Gr5. Granulated I. HUMET specimen (3.7 mg Fe/kg, humic a. 176 mg/kg), animals on ID diet	40 animals
Gr6. Granulated II. HUMET specimen (3.7 mg Fe/kg, humic a. 938 mg/kg), animals on ID diet	40 animals
Gr7. Dried HUMET specimen (3.7 mg Fe/kg, humic a. 112 mg/kg) , animals on ID diet	40 animals

Measured parameters:

Weekly (dams and pups): body weight, relative body weight gain, food consumption.

Once: litter size, perinatal index, survival index

On days 0, 7, 14, 21 : Hematological and serum chemical parameters: RBC, WBC, Platelets, Hb, HT, MCV, MCH, MCHC, ZP (Zinc-protoporfirin/hem ratio), Se Fe , TIBC (total iron binding capacity), AST (GOT), ALT (GPT), triglicerides

Remark: 0 day means the day of weaning

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

National Occupational Health Institute,1094 Budapest Nagyvárad tér 2.., Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company : HORIZON-MULTIPLAN Ltd.	TABULATED STUDY REPORT	
Name of Finished Product : HUMET-R SYRUP	ref.to III.F.110	
Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	Page / Number 2/ 4	
PHARMACODYNAMICS relating to proposed indication	Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups	

Ref. to document : 42-1-11 Volume : Page : — to — Addendum No. :—

Report date : April 29 1997 Number : Study period (years) : 1997

The most important details of the results: Offspring's body weight (g, means only)

Days	0 (n)	7 (n)	14 (n)	21 (n)
Gr1. Normal control	40.74 (40)	66.26 (40)	112.03 (33)	154.71 (17)
Gr2. Iron deficient negative control	22.37 (40)	32.05 (40)	50.71 (32)	45.29 (16)
Gr3. Aktiferrin positive control	21.37 (40)	38.53 (35)	78.83 (25)	112.14 (15)
Gr4.	21.23 (40)	37.74 (35)	71.9 (25)	104.33 (15)
GR5	22.89 (40)	36.97 (33)	66.12 (22)	101.89 (12)
Gr6.	21.46 (40)	37.5 (34)	70.33 (22)	113.58 (12)
Gr7.	22.54 (40)	36.59 (35)	69.42 (23)	105.7 (13)

* = P < 0.05 compared to the iron deficient control

** = p < 0.01 compared to the iron deficient control

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

National Occupational Health Institute, 1094 Budapest Nagyvárad tér 2..., Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company : HORIZON-MULTIPLAN Ltd.	TABULATED STUDY REPORT	
Name of Finished Product : HUMET-R SYRUP	ref.to III.F.110	
Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	Page / Number 3 / 4	
PHARMACODYNAMICS relating to proposed indication	Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups	

Ref. to document : 42-1-11 Volume : Page : — to — Addendum No. :—

Report date : April 29 1997 Number : Study period (years) : 1997

		RBC (T/l, means only)		Hb (g/100 ml, means only)		Se Fe (µmol/l, means only)		TIBC (µmol/l, means only)	
Days	Groups	0 (n)	21 (n)	0 (n)	21 (n)	0 (n)	21 (n)	0 (n)	21 (n)
	Gr1. Normal control	4,52 (7)	5.57 (12)	9.53 (n)	12.9 (n)	59.36 (n)	61.95 (n)	90.20 (n)	82.71 (n)
	Gr2. Iron deficient negative control		6.04 (12)		9.72 (12)		12.47 (12)		115.88 (12)
	Gr3. Aktiferrin positive control		5.46 * (15)		12.43 ** (15)		53.54 ** (15)		82.31 ** (15)
	Gr4.		5.24 ** (15)		12.54 ** (15)		46.5 ** ♣♣ (15)		79.04 ** (15)
	Gr5.	2.57 ♣♣ (6)	5.63 (12)	3.72 ♣♣ (n)	12.08 ** ♣♣ (12)	6.52 ♣♣ (n)	56.71 ** (12)	187.70 ♣♣ (n)	84.93 ** (12)
	GR6		5.54 (12)		11.23 * ♣ (12)		68.99 ** (12)		98.72 **♣ (12)
	Gr7.		5.55 (13)		11.92 ** ♣♣ (13)		70.78 ** (13)		90.00 **♣ (13)

* = P < 0.05 compared to the iron deficient control

** = p < 0.01 compared to the iron deficient control

♣ = P < 0.05 compared to the untreated control

♣♣ = P < 0.01 compared to the untreated control

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

National Occupational Health Institute.1094 Budapest Nagyvárad tér 2... Hungary. EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company : HORIZON-MULTIPLAN Ltd.	TABULATED STUDY REPORT	
Name of Flaished Product : HUMET-R SYRUP	ref.to III.F.110	
Name of Active Ingredient : Humic acid. Potassium. Magnesium. Iron. Zinc. Manganese. Copper. Vanadium. Cobalt. Molybdenum. Selenium	Page / Number 4 / 4	
PHARMACODYNAMICS relating to proposed indication	Study on the effects of different formulations of humic acid bound with iron and other micro elements in iron deficient rat pups	

Ref. to document : 42-1-11 Volume : Page : — to — Addendum No. :—

Report date : April 29 1997 Number : Study period (years) : 1997

		AST (GOT) U/l. means an sly	Trigliceride. (mmol / l. means only)
Days	Groups	21 (n)	21 (n)
	Gr1. Normal control	100.58 (12)	1.17 (n)
	Gr2. Iron deficient negative control	233.27 (12)	0.48 (12)
	Gr3. Aktiferrin positive control	146.58** ♣♣ (15)	0.58 ♣♣ (15)
	Gr4.	160.36** ♣♣ (15)	1.1 * (15)
	Gr5.	152.2** ♣♣ (12)	1.04 * (12)
	GR6	162.75** ♣♣ (12)	0.61 ♣♣ (12)
	Gr7.	153.92** ♣♣ (13)	0.64 ♣♣ (13)

* = P < 0.05 compared to the iron deficient control

** = p < 0.01 compared to the iron deficient control

♣ = P < 0.05 compared to the untreated control

♣♣ = P < 0.01 compared to the untreated control

Conclusions:

All formulas of the macro and micro elements supplemented humic acid proved to be effective in improvement the general status and laboratory parameters in iron deficient animals. The effect was comparable to Aktiferrin. The best result was achieved by the HUMET-R Syrup treatment (Gr4.). Even the serum trigliceride level normalised in this group up to the end of the study, while it left low after the Aktiferrin treatment.

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

National Occupational Health Institute.1094 Budapest Nagyvárad tér 2... Hungary. EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.P.110 Page / Number 1/ 2	

PHARMACODYNAMICS in vivo relating to proposed indication

Report on the pharmacocinetic studies of ^{85}Sr- and ^{103}Ru-humic acid complex in rats

Ref. to document : HUM 015 Volume : Page : — to — Addendum No. :—
Report date : Marc 30.1993 Number : Study period (years) : 1993

Experimental designe:

Group	Treatment	Dose	Dose frequency	Route	No of F/M	Measuring points (hours)	Subjects
1.	$^{85}SrCl_2$ sol.	250 µ/kg	1	p.o.	3-3	24, 48, 72, 96	Metabolic balance (radioactivity in faces and urine)
2.	$^{85}SrCl_2$-Humic acid complex	250 µ/kg 150 mg/kg	1	p.o.	3-3	24, 48, 72, 96	Metabolic balance (radioactivity in faces and urine)
3	$^{85}SrCl_2$ sol.	250 µ/kg	1	i.p.	5-5	24, 48, 72, 96	Metabolic balance (radioactivity in faces and urine)
4.	$^{85}SrCl_2$ sol. Humic acid	250 µ/kg 150 mg/kg	1 1 (after 24h)	i.p, p.o.	5-5	24, 48, 72, 96	Metabolic balance (radioactivity in faces and urine)
5	$^{85}SrCl_2$ sol. Humic acid	250 µ/kg 150 mg/kg	1 4 (in every 24 h)	i.p. p.o.	5-5	24, 48, 72, 96	Metabolic balance (radioactivity in faces and urine)
6.	$^{85}SrCl_2$ sol.	250 µ/kg	1	p.o.	33	0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96	Radioactivity in tissues of 16 organs (3 animals/point)
7	$^{85}SrCl_2$-Humic acid complex.	250 µ/kg 150 mg/kg	1	p.o.	33	0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96	Radioactivity in tissues of 16 organs (3 animals/point)
8.	^{103}Ru sol.	90.9 mg/kg	1	p.o.	5-5	24, 48, 72, 96	Metabolic balance (radioactivity in faces and urine and organs (96h)
9.	^{103}Ru- Humic acid complex	90.9 mg/kg 320mg/kg	1	p.o.	5-5	24, 48, 72, 96	Metabolic balance (radioactivity in faces and urine and organs (96h))

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

Central Isotope Laboratory, Semmelweis University of Medicine, Nagyvárad tér 4., H-1089 Budapest, Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.F.1.1.0 Page / Number 2/ 2	

PHARMACODYNAMICS in vivo relating to proposed indication	Report on the pharmacocinetic studies of ^{85}Sr- and ^{103}Ru-humic acid complex in rats

Ref. to document : HUM 015 Volume : Page : — to — Addendum No. :—
Report date : Marc 30.1993 Number : Study period (years) : 1993

Conclusions

Group 1-2:

The cumulative urinary excretion of $^{85}SrCl_2$ treated animals at 96 hours: 2,87 ± 0,65 (% of dose)

The cumulative urinary excretion of ^{85}Sr-Humic a. complex treated animals at 96 hours: 1,59± 0,42 (% of dose). Explanation: Less amount of ^{85}Sr was absorbed from the complex than from the solution.

Less quantity of radioactivity was eliminated via the stool in the first 24 hours in animals treated with ^{85}Sr-Humic a. complex. By 96 hours the difference between the two groups eliminated.

Group 3-5:

The oral administration of humic acid (once or repeatedly) did not influence the urinary and faecal excretion of ^{85}Sr.

Group 6-7:

Significant less ^{85}Sr incorporated in to the bones at ^{85}Sr-Humic a. complex treated animals than the $^{85}SrCl_2$ solution treated ones.

Group 8-9:

There were no detectable difference in urinary and faecal excretion of ^{103}Ru between the animals treated with the ^{103}Ru salt solution alone or with the ^{103}Ru -complex.
Less amount of radioactivity was found in the tissues of animals treated with the complex preparation, than in the control

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

Central Isotope Laboratory, Semmelweis University of Medicine, Nagyvárad tér 4., H-1089 Budapest. Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.F.1.10 Page / Number 1/ 2	

PHARMACODYNAMICS relating to proposed indication	Cardioprotective effects of SHA and HA preparations in the isolated working rat heart subjected to ischemia/reperfusion.

Ref. to document : HUM 39-1-08 Volume : Page : — to — Addendum No. :---
Report date : June 3 1997 Number : Study period (years) : 1997

Experimental design:

Group 1. vehicle control	No 8	25 min. ischemia + 10 min. reperfusion
Group 2. SHA treatment 10 mg/kg for 2 weeks	No 8	25 min. ischemia + 10 min. reperfusion
Group 3. SHA treatment 30 mg/kg for 2 weeks	No 8	25 min. ischemia + 10 min. reperfusion
Group 4. HA treatment 30 mg/kg for 2 weeks	No 8	25 min. ischemia + 10 min. reperfusion

SHA: macro and elements supplemented humic acid

HA: humic acid

Conclusions:

1. HA and SHA have no effect on the nonischemic myocardium
2. HA has some beneficial effect on myocardial perfusion after ischemia and slight improves myocardial function.
3. SHA 10 mg/kg shows moderate cardioprotective and strong antiarrhitmic effect in the rat heart.
4. SHA 30 mg/kg although results in a tendency of cardioprotection and antiarrhytmic effect but the dose seems to be to high for 2 weeks treatment

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

Dep. Biochemistry, Biological Research Centre, 6726 Szeged Temesvári Krt. 62., Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company : HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	TABULATED STUDY REPORT ref.to III.F.110 Page / Number 1/2	

PHARMACODYNAMICS relating to proposed indication — Cardioprotective effects of SHA and HA preparations in the isolated working rat heart subjected to ischemia/reperfusion.

Ref. to document : HUM 39-1-08 Volume : Page : — to — Addendum No. :—
Report date : June 3 1997 Number : Study period (years) : 1997

Resultes:

Group	No	HR (bpm)		CF (ml/min)		AF (ml/min)		LVDP (kPa)	
		Before ischemia	After ischemia	Before ischemia	After ischemia	Before ischemia	After ischemia	Before ischemia	After ischemia
Control	8	265±6	260±9.9	22.9±0.9	20.4±0.9	43.4±1.5	13.3±2.5	19.2±0.7	14.0±0.5
SHA 10 mg/kg	8	264±7	257±6	24.4±0.8	24.3±0.9 *	43.9±1.7	15.4±2.3	19.3±0.5	14.8±0.7
SHA 30 mg/kg	8	270±4	263±3	23.4±0.9	24.5±0.8 *	44.5±1.4	24.5±2.8 *	19.1±0.4	15.9±0.8
HA 30 mg/kg	8	263±7	257±5	23.0±0.9	23.7±0.9 *	44.9±1.6	19.1±3.6	19.0±0.6	15.3±0.7

Group	No	$+dP/dt_{max}$ (kPa/s)		$-dP/dt_{min}$ (kPa/s)		LVEDP (kPa)		VF (%)	
		Before ischemia	After ischemia	Before ischemia	After ischemia	Before ischemia	After ischemia	Before ischemia	After ischemia
Control	8	10265±45	609±53	463±33	304±20	0.51±0.04	1.53±0.09	-	87.5
SHA 10 mg/kg	8	1058±43	675±35	470±26	339±23	0.54±0.05	1.35±0.07	-	62.5
SHA 30 mg/kg	8	983±41	788±36*	451±20	351±20	0.56±0.05	1.08±0.08	-	12.5 *
HA 30 mg/kg	8	1044±45	708±44	445±21	340±14	0.49±0.04	1.25±0.08	-	37.5

Abbreviations: HR (bpm): heart rate, CF (ml/min) coronary flow, AF (ml/min) aortic flow, LVDP (kPa) left ventricular developed pressure, $+dP/dt_{max}$(kPa/s) and $-dP/dt_{min}$ (kPa/s) maximum and minimum of first derivate of left ventricular pressure, LVEDP (kPa) left ventricular end-diastolic pressure, VF (%) ventricullar fibrillation, *($p<0,05$)

Study conducted by the applicant : [ ] Yes [x] No
If "no", indicate the name and address of the institute that conducted the study :
Dep. Biochemistry, Biological Research Centre, 6726 Szeged Temesvári Krt. 62., Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

Name of Company:	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product: HUMET-R SYRUP Name of Active Ingredient: Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.F.110 Page / Number 1/1	

PHARMACODYNAMICS In vivo relating to proposed indication

OBSERVATION OF THE EFFECTS OF HUMET DERIVATES ON MALE RAT'S SEXUALLITY

Ref. to document : HUM 013 Volume : Page : — to — Addendum No. :—
Report date : November1994 Number : Study period (years) : 1994

Sexual inactivity can be reached by long term 'deprivation' which makes adult male rats chronically unable to display the complete sexual behavioural pattern (mounting, intromission, ejaculation) even if a receptive female is present:

After the above mentioned deprivation sexually inactive males were selected for HUMET-R Syrup treatment.

Sexual inactivity was confirmed at male rats who did not show any reaction (mounting, intromission, ejaculation) in the presence of recipient female one after the other four challenges.

Frequency of challenges: once a week for 30 minutes

Results:

Groups	Number of males responded/ tested	1-4 weeks selection period			1-15 week treatment period			16-30 weeks post-treatment			Latency in responded males weeks
		Mountings	Intromission	Ejaculations	Mountings	Intromission	Ejaculations	Mountings	Intromission	Ejaculations	
5% glucose control 1 ml / day	2/10	0	0	0	83	34	7	0	0	0	3,4 resp.
HUMET-R Syrup 1 ml / day	8/8	0	0	0	408	253	19	237	133	21	1,3,4,4,4,11,13,17 resp.

Conclusions HUMET-R Syrup was found highly efficient in recovering sexual activity. The recovered activity was kept long after the last treatment

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :

Pharm Expert Association, Pharmaceutical Institute, Semmelweis University of Medicine, Nagyvárad tér 4., H-1089 Budapest, Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required

CURRICULUM VITAE

Name: Dr László Német

Date of Birth : 2nd February 1951

Place of Birth: Budapest, Hungary

Family: married

Professional Expetience:

Pharmacological Research Institute for Drug Research 1974-80
1974-75 Associate Research Fellow
1975-80 Head of Dog Toxicology Plant at Dunakeszi

Chemical Works of Gedeon Richter Ltd., 1980-1997
1980-88 Toxicological Laboratory
Toxico-pathologist
1988-95 Pathological Laboratory
Pathologist and head of the laboratory
1995-97 Preclinical Development, Director of Dug Safety Laboratories :
General Toxicology, Reproductive Toxicology, Pathology,
Pharmaco-Kinetics

State Control Institute for Veterinary Biologicals, Drugs and Feeds
1997- Pharmacological Department
Official in charge of approval of veterinary medical products

Education: 1969-74 University of Veterinary Science , Budapest.
Graduation: Doctor of Veterinary Medicine 1974

Postgraduate Courses:

1978-80 Training in Toxicology,
Postgraduate School of Veterinary Science, Budapest.
Graduation: Veterinary Toxicologist 1980

One month fellowship in immuno-histochemie at the Pathological Institute of Veterinary University of Vienna, 1983

Training in Human Pathology
Postgraduate School of Medicine,
Budapest, 1987-88

One month fellowship in Frauenhofer
Institut für Toxikologie und Aerosolforschung,
Hannover, 1990

Histopathology Seminar on the Musculoskeletal
System of Laboratory Animals, Hannover
September 4-6 1990

Histopathology Seminar on the Special Senses of
Laboratory Animals, Hannover September 4-6 1991

BSTP Training Course in Toxicological Pathology
Pathology of the liver, Cambridge
March 1994

IUPHAR Workshop on Biological Monitoring of Chemical Exposure,
New Delhi Dec. 1997

Professional Societies:
Hungarian Society of Pathologists
Union of Hungarian Toxicologists
Hungarian Association of Laboratory Animal Sciences

Language : German, English

PC Skills: Excel, Win-Word, PowerPoint, Statistica

Number of presentations and publications : 24

Consulting lectures: 14

Budapest, 28th January, 1999

Consulting Lectures

A szem toxikológiája (Toxikology of Eyes)
OTE posztgraduális toxikológus képzés
(Postgraduate School of Medicine, Seminar for
Toxicologists), Budapest, 1984

A krónikus toxikológiai vizsgálat
(The Chronic Toxicological Study)
OTE posztgraduális toxikológus képzés
(Postgraduate School of Medicine, Seminar for
Toxicologists), Budapest, 1984

Good Laboratory Practice a gyógyszerbiztonsági vizsgálatokban.
(The GLP in the safety studies.)
Szabvány müveleti eljárások készítése,
használata, karbantartása.
(Creating, using and maintaining SOPs.)
Budapesti Müszaki Egyetem Mérnöktovábbképzõ
Intézet. (Engineering Postgraduate Training
Institute) Budapest, 1991

Good Laboratory Practice a gyógyszerbiztonsági vizsgálatokban.
(The GLP in the safety studies.)
A patológiai laboratórium és az archivum szervezése.
(How to organize the pathological laboratory and archive.)
Budapesti Müszaki Egyetem Mérnöktovábbképzõ Intézet
(Engineering Postgraduate Training Institute.)
Budapest, 1991

Gyógyszerész szakvizsga elõkészítõ.
(Training course for pharmacists.)
A patológia szerepe a gyógyszerbiztonsági vizsgálatokban.
(The role of pathology in safety studies.)
OGYI / National Institute of Pharmacy.
Budapest, from 1991 annually up to 1997

Az Európa Tanács állásfoglalása a kísérleti állatok védelméről
(European Convention for the Protection of
vertebrate animals.....)
OTE Experimentális Toxikológia, posztgraduális képzés
(Postgraduate School of Medicine, Experimental
Toxicology), Budapest, 1991

Laborállatok tartása, kezelése
(Animal care, research)
OTE Experimentális Toxikológia, posztgraduális képzés
(Postgraduate School of Medicine, Experimental
Toxicology), Budapest, 1991

Állattenyésztés, állathigiénia
(Animal breeding, animal hygiene)
OTE Experimentális Toxikológia, posztgraduális képzés
(Postgraduate School of Medicine, Experimental
Toxicology), Budapest, 1991

Laborállatták
(Animal diets)
OTE Experimentális Toxikológia, posztgraduális képzés
(Postgraduate School of Medicine, Experimental Toxicology),
Budapest, 1991

Laboratóriumi állatok fertőző betegségei
(Infectious diseases of laboratory animals)
OTE Experimentális Toxikológia, posztgraduális
képzés
(Postgraduate School of Medicine, Experimental
Toxicology), Budapest, 1991

Laboratóriumi állatok higiéniai állapotának
minősítése és betegségeik
(accreditation of animal health status and
diseases of laboratory animals)
ÁOTE szakosított továbbképző tanfolyam
(Postgraduate Course of Veterinary University)
Budapest, from 1992 annually

A patológia szerepe a preklinikai gyógyszerbiztonsági vizsgálatokban
(The role of Pathology in preclinical safety development)
DOTE kliniko-farmakológus tanfolyam
(Postgraduate School of Medicine, Clinical-Pharmacological Course)
Debrecen, 1995

Rágcsálók és nyúlajkuak anatómiai jellegzetességei
(Anatomical caracteristics of rodents and lagomorphs)
A patológia alapfogalmai
(Basic concepts in pathology)
Laboratóriumi állatok fertőzőbetegségei
(Infectious diseases of laboratory animals)
Posztgraduális toxikológus képzés négy szemeszterben (Postgraduate Lectures in
Toxicology),
Állatorvostudományi Egyetem Továbbképzési központ (Postgraduate School of
Veterinary University), Budapest, 1997

A toxiko-patológiai laboratórium GLP szervezése.
(The GLP organisation in the toxico-pathological laboratory.)
Felfüggesztett gyógyszerfejlesztések kóroktani szempontból. Eset tanulmányok.
(Suspended drug developments from general pathological aspects. Case studies.)
Posztgraduális toxikológus képzés négy szemeszterben (Postgraduate Lectures in Toxicology),
Állatorvostudományi Egyetem Továbbképzési központ (Postgraduate School of Veterinary University), Budapest. 1998

Budapest, 28th January, 1999

Addendum to the "Expert Report on the Pharmaco-Toxicological (Pre-Clinical) Documentation of Humet-R Syrup (1999)

2000

Compiled by László Német DVM, PhD.

Introduction

Because of the increasing demand of the market and with the development of manufacturing technology, two solid forms (HUMET Turbo Capsule and Humetta Effervescent Tablet) were developed of the original liquid HUMET-R Syrup.

The recommended daily oral dose for adults is 10 ml of HUMET-R Syrup which is equivalent with 75 mg humic acid (about 1 mg/kg human daily dose). The new solid products contain 1/3 of the liquid syrup which is equivalent with 25 mg humic acid pro capsule or tablet.

An additional toxicological study was conducted by feeding the active ingredient (potassium humate) in solid (powder) form with rats for 60 days, to prove the similarity of the toxicological profile of liquid and solid forms in repeated doses.

60-Day Toxicological Study of a Powder Humic Acid Product in Rats

(See: Tabulated study report Page 1, Addendum 1)

In the 60-day non GLP repeated dose study, the active ingredient; potassium humate was mixed in powder form to normal rat food in order to achieve a daily 60 and 240 mg/kg intake which is corresponds to 60 and 240-fold of the human dose The food consumption was calculated for an average of 20g food / animal / day. The control group was supplied by normal rat food. Only female animals were used, 16 in the control group and 20-20 in potassium humate fed groups.

Accoding to the protocol five-five animals were sacrificed from each group on weak 2, 4, 6 and 8. Animals were observed daily, body weight was measured weekly, and parameters of hematology and organ weights were measured at the time of necropsy.

Deviations from a regular type repeated dose toxicity study is the following: Study design, only one sex was used. Measuring of food consumption, water consumption, of clinical chemistry urinalysis and histological evaluation were not employed.

No death occurred during the treatment. Body weight decreased slightly from the 4rd week of treatment up to the end of study in the 60 mg/kg treated group, while the mean body weight remain comparable to the control in the 240 mg/kg group. No other significant changes occurred in the parameters of hematology or organ weights.

In the previous 28-day repeated dose study of HUMET-R Syrup in rats NOEL and NOAEL were estimated over the oral 50 mg/kg dose, based on the lowered body weights in female rats.

Oct 7. 2000.

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd Name of Finished Products : HUMET-Turbo Caps. and HUMETTA Tabl. Name of Active Ingredient : Potassium humate	STUDY REPORT ref. to III.B.110 Page / Number 1 / 1	

REPEATED DOSE TOXICITY	60-Day Toxicological Study of a Powder Humic Acid Product in Rats

Ref. to document : HUM 057 **Volume:** **Page :** --- **to** --- **Addendum No. :** ---
Report date : March 30 1994 **Number :** **Study period (years) :** 1998

Species/Strain : RAT, WISTAR Females

Number of animals : 56	**Duration of treatment :** 60 days
Observation period after the end of dosing : 0	
Administration route: by food	
Treatment of controls : Group 1: Untreated, on normal food	**Age :** at study **Body weight :** 170-190 g initiation **Treatment days per week :** 7

Study group	control	Humet-powder 60 mg/kg	Humet powder 240 mg/kg
Sex (m/f)	f	f	f
Number of test animals	16	20	20
Number of animals died Or sacrificed in extremis	0	0	0

Clinical observations :	[x] yes	[ ] no	**Clinical chemistry :**	[ ] yes	[x] no
Food consumption :	[ ] yes	[x] no	**Urinalysis :** –	[ ] yes	[x] no
Water consumption :	[ ] yes	[x] no	**Organ weights :**	[x] yes	[ ] no
Body weight :	[x] yes	[ ] no	**Necropsy :**	[x] yes	[ ] no
Hematology:	[x] yes	[ ] no	**Histology :**	[ ] yes	[x] no

Additional information: Doses were calculated for an average of 20g food consumption / animal / day
Five-five animals were sacrificed from each group on weak 2, 4, 6 and 8.

Conclusions: - **Body weight decreased from the 4th week up to the end of study in 60 mg/kg treated group.**

Histology performed according to EEC Note for Guidance : [ ] Yes [x] No
Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Dep. of Toxicology, Health Institute of Hungarian Army, 1456 Budapest, Pf. 19., Hungary, Europe

Study in compliance with GLP : [ ] Yes [x] No [ ] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.D.110 Page / Number 3 / 5	

MUTAGENIC POTENTIAL	In vitro	REVERSE MUTATION IN SALMONELLA THYPHIMURIUM

Ref. to document : HUM 008 Volume : Page : — to — Addendum No. :—
Report date : 1 Oct. 1992 Number : 92/134-007M Study period (years) : 1992

Test cells :	SALMONELLA THYPHIMURIUM TA 1535
Test for induction of :	base substitution and frameshift point mutation
Metabolizing system :	Aroclor 1254 induced rat liver S 9-mix

Formulation of test substance and final concentration :	a) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate
Treatment and recovery time :	a) 48 hours, no recovery time b) 48 hours, no recovery time
Solvent and Final concentration :	a) 1% aqueous potassium-pyrophosphate b) 1% aqueous potassium-pyrophosphate
Formulation of positive Control and final Concentration	a) Sodium azide; 4 µg/plate b) 2-Aminoanthracene; 4 µg/plate

Number of independent experiments : a) 2 (without metabolic activitation) b) 2 (with metabolic activitation)	Number of replicate cultures : a) 3 plates per concentration b) 3 plates per experiments
Number of cells analysed per culture :	a) — b) —

Cytotoxic effects :
a) —
b) —
Genotoxic effects :
a) The test substances did not induce increases in the number of revertant colonies
b) Similar to the control values at any dose-level, either in the absence or presence of S9 metabolism
Effects of the positive control :
a) 589 plate counts (exp.1) resp. 588 (exp.2); solvent control 14 (exp.1) resp. 14 (exp.2)
b) 1486 plate counts (exp.1) resp. 559 (exp.2); solvent control 15 (exp.1) resp. 15 (exp.2)

Additional data regarding methods and time schedule of the test :
-Test item was the lyophised form of the finished productwith a 78.5 g/l of dry remnant content
-To demonstrate mutagenic effect the concentration of S9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study.

Study conducted by the applicant : [ ] Yes [x] No
If "no", indicate the name and address of the institute that conducted the study :
Toxicological Research Centre Ltd. Szabadságpuszta Veszprém H-8200 Hungary EUROPE

Study in compliance with GLP : [x] Yes [ ] No [ ] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.D.110 Page / Number 4 / 5	

MUTAGENIC POTENTIAL **In vitro** REVERSE MUTATION IN SALMONELLA THYPHIMURIUM

Ref. to document : HUM 008 **Volume :** **Page :** — **to** — **Addendum No. :**—
Report date : 1 Oct. 1992 **Number :** 92/134-007M **Study period (years) :** 1992

Test cells :	SALMONELLA THYPHIMURIUM TA 1538
Test for induction of :	base substitution and frameshift point mutation
Metabolizing system :	Aroclor 1254 induced rat liver S 9-mix

Formulation of test substance and final concentration :	a) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate
Treatment and recovery time :	a) 48 hours, no recovery time b) 48 hours, no recovery time
Solvent and Final concentration :	a) 1% aqueous potassium-pyrophosphate b) 1% aqueous potassium-pyrophosphate
Formulation of positive Control and final Concentration	a) 4-nitro-o-phenilenediamine; 4 µg/plate b) 2-Aminoanthracene; 4 µg/plate

Number of independent experiments :
a) 2 (without metabolic activitation)
b) 2 (with metabolic activitation)

Number of replicate cultures :
a) 3 plates per concentration
b) 3 plates per experiments

Number of cells analysed per culture :
a) ---
b) ---

Cytotoxic effects :
a) ---
b) ---

Genotoxic effects :
a) The test substances did not induce increases in the number of revertant colonies
b) Similar to the control values at any dose-level, either in the absence or presence of S9 metabolism

Effects of the positive control :
a) 976 plate counts (exp.1) resp. 625 (exp.2); solvent control 13 (exp.1) resp. 17 (exp.2)
b) 415 plate counts (exp.1) resp. 421 (exp.2); solvent control 19 (exp.1) resp. 23 (exp.2)

Additional data regarding methods and time schedule of the test :
-Test item was the lyophised form of the finisched productwith a 78.5 g/l of dry remnant content
-To demonstrate mutagenic effect the concentration of S9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study.

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Toxicological Research Centre Ltd. Szabadsigpuszta Veszprém H-8200 Hungary EUROPE

Study in compliance with GLP : [x] Yes [ ] No [ ] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.D.110 Page / Number 5 / 5	

MUTAGENIC POTENTIAL	In vitro	REVERSE MUTATION IN SALMONELLA THYPHIMURIUM

Ref. to document : HUM 008 Volume : Page : — to — Addendum No. :—
Report date : 1 Oct. 1992 Number : 92/134-007M Study period (years) : 1992

Test cells :	SALMONELLA THYPHIMURIUM TA 1537
Test for induction of :	base substitution and frameshift point mutation
Metabolizing system :	Aroclor 1254 induced rat liver S 9-mix

Formulation of test substance and final concentration :	a) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate b) solution: 468.75, 937.5, 1875, 3750, 7500 µg/plate
Treatment and recovery time :	a) 48 hours, no recovery time b) 48 hours, no recovery time
Solvent and Final concentration :	a) 1% aqueous potassium-pyrophosphate b) 1% aqueous potassium-pyrophosphate
Formulation of positive Control and final Concentration	a) 9-aminoacridine; 50 µg/plate b) 2-Aminoanthracene; 4 µg/plate

Number of independent experiments :
a) 2 (without metabolic activitation)
b) 2 (with metabolic activitation)

Number of replicate cultures :
a) 3 plates per concentration
b) 3 plates per experiments

Number of cells analysed per culture :
a) —
b) —

Cytotoxic effects :
a) —
b) —

Genotoxic effects :
a) The test substances did not induce increases in the number of revertant colonies
b) Similar to the control values at any dose-level, either in the absence or presence of S9 metabolism

Effects of the positive control :
a) 1958 plate counts (exp.1) resp. 253 (exp.2); solvent control 24 (exp.1) resp. 23 (exp.2)
b) 1765 plate counts (exp.1) resp. 312 (exp.2); solvent control 24 (exp.1) resp. 29 (exp.2)

Additional data regarding methods and time schedule of the test :
-Test item was the lyophised form of the finisched productwith a 78.5 g/l of dry remnant content
-To demonstrate mutagenic effect the concentration of S9 fraction was increased up to 30 % and a 30 minutes preincubation time was established in the second study.

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Toxicological Research Centre Ltd. Szabadságpuszta Veszprém H-8200 Hungary EUROPE

Study in compliance with GLP : [x] Yes [ ] No [ ] Not required

Name of Company :	TABULATED	
HORIZON-MULTIPLAN Ltd. Name of Finished Product : HUMET-R SYRUP Name of Active Ingredient : Humic acid, Potassium, Magnesium, Iron, Zinc, Manganese, Copper, Vanadium, Cobalt, Molybdenum, Selenium	STUDY REPORT ref.to III.D.110 Page / Number 1 / 2	

MUTAGENIC POTENTIAL	In vitro	ANTI-CLASTOGENIC EFFECT OF HUMET_R IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES

Ref. to document : HUM 004 Volume : Page : --- to --- Addendum No. :---
Report date : 1992 Number : Study period (years) : 1992

Test cells :	Peripheral human lymphocytes
Test for induction of :	Chromosomal aberration
Metabolizing system :	Non

Formulation of test substance And final concentration :	a) solution: 10, 20, 100, 200 µl / ml culture b)
Treatment and Recovery time :	a) 48 hours incubation b)
Solvent and Final concentration :	a) media: 10 ml RPMI-1640 + 0,8 ml blood + 0.2 ml Phytohemagglutinin M to prepare cell division, after 48 hour colcemide 0.1 µg/ml to stop the cell division b)
Formulation of positive Control and final Concentration	a) N /A b)

Number of independent experiments :
a) 2
b)

Number of replicate cultures :
a)
b)

Number of cells analysed per culture : a) 600 in control, 200 in treated groups-
b) ---

Genotoxic effects : Aberrations of chromosomes %

		Chromatid break	chromosome break	dicentric chromosoma	aberrant cell
	control	0	1	0	1
Humet	10 µl / ml	0	0	0	0
Humet	20 µl / ml	1	0	0	0
Humet	100 µl / ml	1	0	0	1
Humet	200 µl / ml	0	0	0	0

Concentrations did not reveal clastogenic effect

Effects of the positive control : a) N /A
b)

Additional data regarding methods and time schedule of the test :

Study conducted by the applicant : [ ] Yes [x] No

If "no", indicate the name and address of the institute that conducted the study :
Department of Human Genetics, Medical Research Institute 1138 Budapest Váci út 174. Hungary, EUROPE

Study in compliance with GLP : [ ] Yes [ ] No [x] Not required